

WHAT IS CLAIMED IS:

1 1. A method for enhancing delivery of a compound into and across an
2 animal ocular tissue, the method comprising:
3 administering to the ocular tissue a conjugate comprising the compound and a
4 delivery-enhancing transporter,

5 wherein:

6 i. the compound is attached to the delivery-enhancing transporter
7 through a linker, and

8 ii. the delivery-enhancing transporter comprises fewer than 50 subunits
9 and comprises at least 5 guanidino or amidino moieties, thereby increasing delivery of the
10 conjugate into the ocular tissue compared to delivery of the compound in the absence of the
11 delivery-enhancing transporter.

1 2. The method of claim 1, wherein delivery of the conjugate into the
2 ocular tissue is increased at least two-fold compared to delivery of the compound in the
3 absence of the delivery-enhancing transporter.

1 3. The method of claim 1, wherein delivery of the conjugate into the
2 ocular tissue is increased at least ten-fold compared to delivery of the compound in the
3 absence of the delivery-enhancing transporter.

1 4. The method of claim 1, wherein the ocular tissue is one or more layers
2 of epithelial or endothelial tissue.

1 5. The method of claim 1, wherein the ocular tissue is the retina.

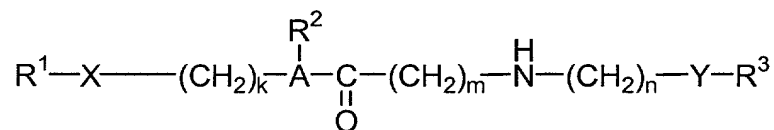
1 6. The method of claim 1, wherein the ocular tissue is the optic nerve.

1 7. The method of claim 1, wherein the linker is a releasable linker.

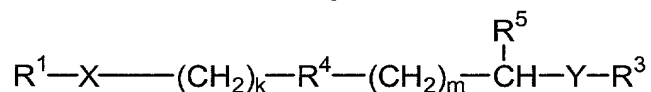
1 8. The method of claim 7, wherein the linker is stable in a saline solution a
2 pH 7 but is cleaved when transported into a cell.

1 9. The method of claim 1, wherein the subunits are amino acids.

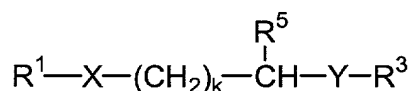
1 10. The method of claim 1, wherein the conjugate has a structure selected
2 from the group consisting of structures 3, 4, or 5, as follows:



3 3



4 4



5 5

6 wherein:

7 R¹ comprises the compound;

8 X is a linkage formed between a functional group on the biologically active
9 compound and a terminal functional group on the linking moiety;

10 Y is a linkage formed from a functional group on the transport moiety and a
11 functional group on the linking moiety;

12 A is N or CH;

13 R² is hydrogen, alkyl, aryl, acyl, or allyl;

14 R³ comprises the delivery-enhancing transporter;

15 R⁴ is S, O, NR⁶ or CR⁷R⁸;

16 R⁵ is H, OH, SH or NHR₆;

17 R⁶ is hydrogen, alkyl, aryl, acyl or allyl;

19 k and m are each independently selected from 1 and 2; and
 20 n is 1 to 10.

1 11. The method of claim 10, wherein X is selected from the group
 2 consisting of -C(O)O-, -C(O)NH-, -OC(O)NH-, -S-S-, -C(S)O-, -C(S)NH-, -NHC(O)NH-,
 3 -SO₂NH-, -SONH-, phosphate, phosphonate phosphinate, and CR⁷R⁸, wherein R⁷ and R⁸ are
 4 each independently selected from the group consisting of H and alkyl.

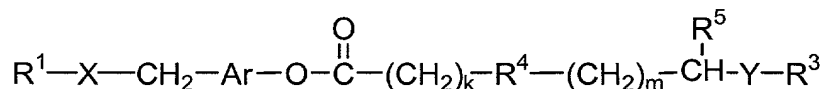
1 12. The method of claim 10, wherein the conjugate comprises structure 3, Y
 2 is N, and R² is methyl, ethyl, propyl, butyl, allyl, benzyl or phenyl.

1 13. The method of claim 10, wherein R² is benzyl; k, m, and n are each 1,
 2 and X is -OC(O)-.

1 14. The method of claim 10, wherein the conjugate comprises structure 4;
 2 R⁴ is S; R⁵ is NHR⁶; and R⁶ is hydrogen, methyl, allyl, butyl or phenyl.

1 15. The method of claim 10, wherein the conjugate comprises structure 4;
 2 R⁵ is NHR⁶; R⁶ is hydrogen, methyl, allyl, butyl or phenyl; and k and m are each 1.

1 16. The method of claim 1, wherein the conjugate comprises structure 6 as
 2 follows:



3 **6**

4 wherein:

5 R¹ comprises the compound;

6 X is a linkage formed between a functional group on the biologically
 7 active compound and a terminal functional group on the linking moiety;

8 Y is a linkage formed from a functional group on the transport moiety
 9 and a functional group on the linking moiety;

10 Ar is an aryl group having the attached radicals arranged in an *ortho* or
 11 *para* configuration, which aryl group can be substituted or unsubstituted;
 12 R³ comprises the delivery-enhancing transporter;
 13 R⁴ is S, O, NR⁶ or CR⁷R⁸;
 14 R⁵ is H, OH, SH or NHR₆;
 15 R⁶ is hydrogen, alkyl, aryl, arylalkyl, acyl or allyl;
 16 R⁷ and R⁸ are independently selected from hydrogen or alkyl; and
 17 k and m are each independently selected from 1 and 2.

1 17. The method of claim 16, wherein X is selected from the group
 2 consisting of -C(O)O-, -C(O)NH-, -OC(O)NH-, -S-S-, -C(S)O-, -C(S)NH-, -NHC(O)NH-,
 3 -SO₂NH-, -SONH-, phosphate, phosphonate phosphinate, and CR⁷R⁸, wherein R⁷ and R⁸ are
 4 each independently selected from the group consisting of H and alkyl.

1 18. The method of claim 16, wherein R₄ is S; R⁵ is NHR⁶; and R⁶ is
 2 hydrogen, methyl, allyl, butyl or phenyl.

1 19. The method of claim 1, wherein the conjugate comprises at least two
 2 delivery-enhancing transporters.

1 20. The method of claim 1, wherein the conjugate is administered as an eye
 2 drop.

1 21. The method of claim 1, wherein the conjugate is administered as an
 2 injection.

1 22. The method of claim 1, wherein the delivery-enhancing transporter
 2 comprises a non-peptide backbone.

1 23. The method of claim 1, wherein the delivery-enhancing transporter is
 2 not attached to an amino acid sequence to which the delivery enhancing transporter molecule
 3 is attached in a naturally occurring protein.

1 24. The method of claim 1, wherein the delivery-enhancing transporter
2 comprises from 5 to 25 guanidino or amidino moieties.

1 25. The method of claim 24, wherein the delivery-enhancing transporter
2 comprises between 7 and 15 guanidino moieties.

1 26. The method of claim 24, wherein the delivery-enhancing transporter
2 comprises at least 6 contiguous guanidino and/or amidino moieties.

1 27. The method of claim 1, wherein the delivery-enhancing transporter
2 consists essentially of 5 to 50 amino acids, at least 50 percent of which amino acids are
3 arginines or analogs thereof.

1 28. The method of claim 27, wherein the delivery-enhancing transporter
2 comprises 5 to 25 arginine residues or analogs thereof.

1 29. The method of claim 28, wherein at least one arginine is a D-arginine.

1 30. The method of claim 29, wherein all of the arginines are D-arginines.

1 31. The method of claim 27, wherein at least 70 percent of the amino acids
2 that comprise the delivery-enhancing transporter are arginines or arginine analogs.

1 32. The method of claim 27, wherein the delivery-enhancing transporter is
2 seven contiguous D-arginines.

1 33. The method of claim 1, wherein the compound is a therapeutic for a
2 disease selected from the group consisting of bacterial infections, viral infections, fungal
3 infections, glaucoma, anterior, intermediate, and posterior uveitis, optic neuritis, Leber's
4 neuroretinitis, retinitis, psudotumor/myositis, orbital myositis, hemangioma/lymphangioma,
5 toxocariasis, behcet's panuveitis, inflammatory chorisretinopathies, vasculitis, dry eye
6 syndrome (Sjogren's syndrome), corneal edema, accommodative esotropia, cycloplegia,
7 mydriasis, reverse mydriasis, and macular degeneracy.

